CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 064120

Trade Name : TRIMETHOPRIM SULFATE AND POLYMYXIN B SULFASTE OPHTHALMIC SOLUTION

Generic Name: Trimethoprim Sulfate and Polymyxin B Sulfate Ophthalmic Solution 1mg(base)/10,000 units per ml

Sponsor : Bausch and Lomb Pharmaceuticals, Inc.

Approval Date: February 14, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 064120

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 064120

APPROVAL LETTER

AADA 64-120

FEB 14 1997

Bausch & Lomb Pharmaceuticals, Inc.
Attention: David B. Desris
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

This is in reference to your abbreviated antibiotic drug application dated December 31, 1993, submitted pursuant to Section 507 of the Food, Drug, and Cosmetic Act, for Trimethoprim Sulfate and Polymyxin B Sulfate Ophthalmic Solution, 1 mg (base)/10,000 units per mL.

Reference is also made to your amendments dated November 15, 1996, November 27, 1996, and January 22, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Trimethoprim Sulfate and Polymyxin B Sulfate Ophthalmic Solution, 1 mg (base)/10,000 units per mL to be bioequivalent, and therefore, therapeutically equivalent to the listed drug, Polytrim® Ophthalmic Solution of Allergan Pharmaceuticals.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

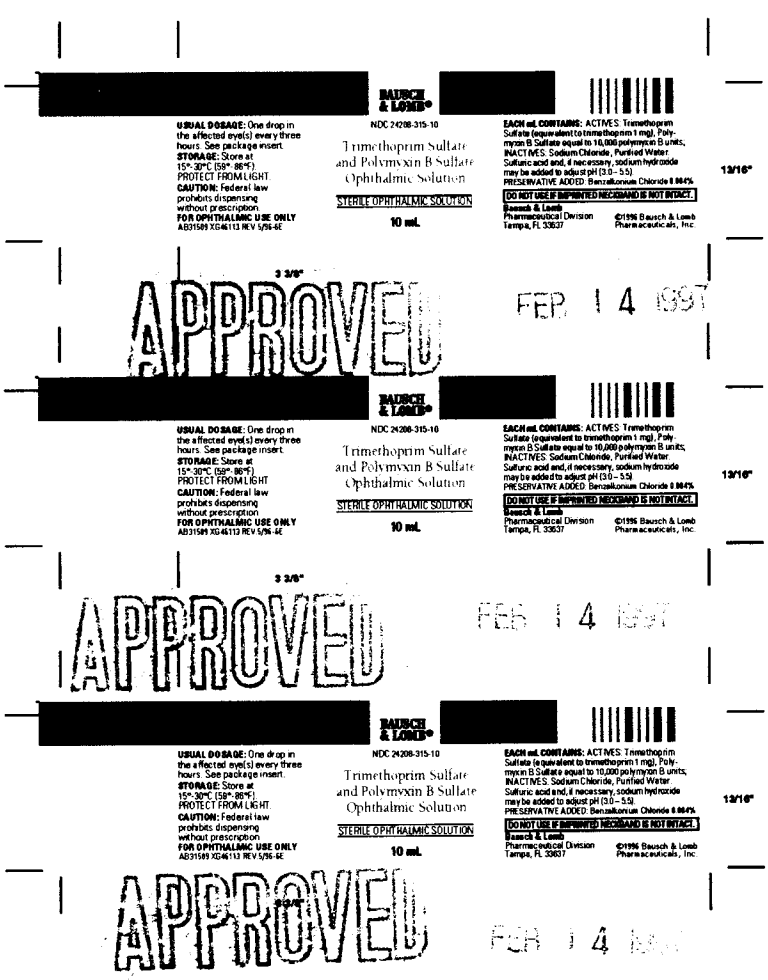
Sincerely yours,

Douglas L. Sporn - 2/14/97
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064120

FINAL PRINTED LABELING


BAUSCH & LOMB®
USUAL DOSAGE: One drop in the affected eye(s) every three hours. See package insert.
STORAGE: Store at 15°-30°C (59°-86°F). PROTECT FROM LIGHT.
CAUTION: Federal law prohibits dispensing without prescription.
FOR OPHTHALMIC USE ONLY
AB31589 XG46113 REV 5/96-6E
NDC 24208-315-10
Trimethoprim Sulfate and Polymyxin B Sulfate Ophthalmic Solution
STERILE OPHTHALMIC SOLUTION
10 mL
EACH mL CONTAINS: ACTIVES: Trimethoprim Sulfate (equivalent to trimethoprim 1 mg), Polymyxin B Sulfate equal to 10,000 polymyxin B units. INACTIVES: Sodium Chloride, Purified Water. Sulfuric acid and, if necessary, sodium hydroxide may be added to adjust pH (3.0 – 5.5). PRESERVATIVE ADDED: Benzalkonium Chloride 0.004%
DO NOT USE IF IMPRINTED NECKBAND IS NOT INTACT.
Bausch & Lomb
Pharmaceutical Division
Tampa, FL 33637
©1996 Bausch & Lomb Pharmaceuticals, Inc.
3 3/8"
13/16"
APPROVED
FEB 14 1997
BAUSCH & LOMB®
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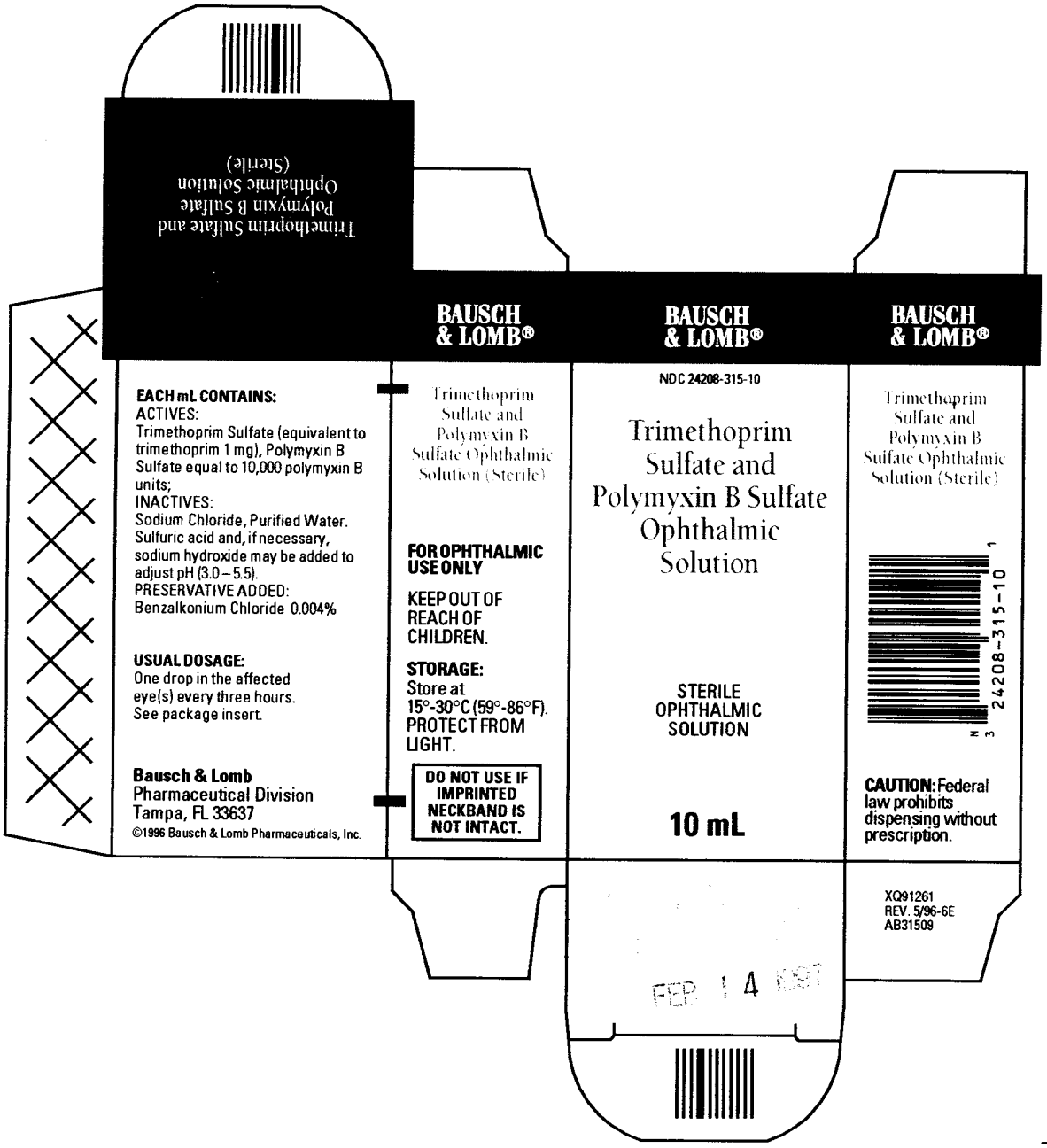
13/16"
APPROVED
FEB 14 1997



CORE 31509 / 10mL CARTON
Art is at 100%
Box Dimensions: 1 5/8" x 1 1/16" x 3 3/8"
3 Color: Black, Process Blue, PMS 467
UPC# 24208-315-10
PHARMACODE #2055
L-2004
SCANNER BAR LOCATIONS: 0.3125" & 2.75" (5 & 44)

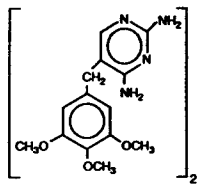
BAUSCH & LOMB®

Trimethoprim Sulfate and Polymyxin B Sulfate Ophthalmic Solution

STERILE OPHTHALMIC SOLUTION

FOR OPHTHALMIC USE ONLY

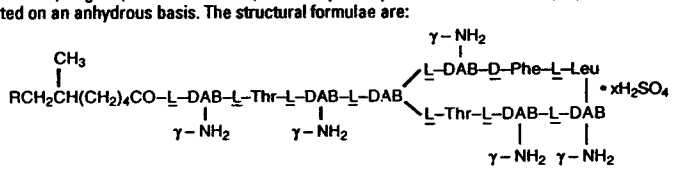
DESCRIPTION:
Trimethoprim Sulfate and Polymyxin B Sulfate Ophthalmic Solution is a sterile antimicrobial solution for topical ophthalmic use. Trimethoprim sulfate, a white, odorless, crystalline powder, is represented by the following structural formula:



$C_{25}H_{32}N_8O_{10}S$ Mol. Wt. 678.72

Chemical Name: Trimethoprim sulfate, 2,4-diamino-5-(3,4 5-trimethoxybenzyl)pyrimidine sulfate (2:1)

Polymyxin B sulfate is the sulfate salt of polymyxin B_1 and B_2 which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6,000 polymyxin B units per mg, calculated on an anhydrous basis. The structural formulae are:



Polymyxin B_1(R = CH_3)
Polymyxin B_2(R = H)
DAB = α, γ-diaminobutyric acid

Each mL Contains: ACTIVES: Trimethoprim Sulfate (equivalent to trimethoprim 1 mg), Polymyxin B Sulfate equal to 10,000 polymyxin B units; INACTIVES: Sodium Chloride, Purified Water Sulfuric acid and, if necessary, sodium hydroxide may be added to adjust pH (3.0 – 5.5). PRESERVATIVE ADDED: Benzalkonium Chloride 0.004%

CLINICAL PHARMACOLOGY:
Trimethoprim is a synthetic antibacterial drug active against a wide variety of aerobic gram-positive and gram-negative ophthalmic pathogens. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. For that reason, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

Polymyxin B, a cyclic lipopeptide antibiotic, is rapidly bactericidal for a variety of gram-negative organisms, especially *Pseudomonas aeruginosa*. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.

When used topically, trimethoprim and polymyxin B absorption through intact skin and mucous membranes is insignificant.

Blood samples were obtained from 11 human volunteers at 20 minutes, 1 hour and 3 hours following instillation in the eye of 2 drops of ophthalmic solution containing 1 mg trimethoprim and 10,000 units polymyxin B per mL. Peak serum concentrations were approximately 0.03 µg/mL trimethoprim and 1 unit/mL polymyxin B.

Microbiology:
In vitro studies have demonstrated that the anti-infective components of trimethoprim sulfate and polymyxin B sulfate ophthalmic solution are active against the following bacterial pathogens that are capable of causing external infections of the eye:

Trimethoprim: *Staphylococcus aureus* and *Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus aegyptius, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* (indole-negative), *Proteus vulgaris* (indole-positive), *Enterobacter aerogenes,* and *Serratia marcescens.*

Polymyxin B: *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes* and *Haemophilus influenzae.*

INDICATIONS AND USAGE:
Trimethoprim sulfate and polymyxin B sulfate ophthalmic solution is indicated in the treatment of surface ocular bacterial infections, including acute bacterial conjunctivitis, and blepharoconjunctivitis, caused by susceptible strains of the following microorganisms: *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus viridans, Haemophilus influenzae* and *Pseudomonas aeruginosa.**
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS:
Trimethoprim sulfate and polymyxin B sulfate ophthalmic solution is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS:
NOT FOR INJECTION INTO THE EYE.
If a sensitivity reaction to trimethoprim sulfate and polymyxin B sulfate ophthalmic solution occurs, discontinue use. Trimethoprim sulfate and polymyxin B sulfate ophthalmic solution is not indicated for the prophylaxis or treatment of ophthalmia neonatorum.

PRECAUTIONS:
General: As with other antimicrobial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers, or other source. This precaution is necessary if the sterility of the drops is to be maintained.

If redness, irritation, swelling or pain persists or increases, discontinue use immediately and contact your physician.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with polymyxin B sulfate or trimethoprim.

Mutagenesis: Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels after oral administration; at concentrations approximately 1000 times human plasma levels after oral administration in these same cells a low level of chromosomal damage was induced at one of the laboratories. Studies to evaluate mutagenic potential have not been conducted with polymyxin B sulfate.

Impairment of Fertility: Polymyxin B sulfate has been reported to impair the motility of equine sperm, but its effects on male or female fertility are unknown.

No adverse effects on fertility or general reproductive performance were observed in rats given trimethoprim in oral dosages as high as 70 mg/kg/day for males and 14 mg/kg/day for females.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with polymyxin B sulfate. It is not known whether polymyxin B sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Trimethoprim has been shown to be teratogenic in the rat when given in oral doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with oral doses 6 times the human therapeutic dose.

While there are no large well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and Pursell, in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or oral trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim may interfere with folic acid metabolism, trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: The oral administration of trimethoprim to rats at a dose of 70 mg/kg/day commencing with the last third of gestation and continuing through parturition and lactation caused no deleterious effects on gestation or pup growth and survival.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trimethoprim sulfate and polymyxin B sulfate ophthalmic solution is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 months have not been established (see WARNINGS).

ADVERSE REACTIONS:
The most frequent adverse reaction to trimethoprim sulfate and polymyxin B sulfate ophthalmic solution is local irritation consisting of increased redness, burning, stinging, and/or itching. This may occur on instillation, within 48 hours, or at any time with extended use. There are also multiple reports of hypersensitivity reactions consisting of lid edema, itching, increased redness, tearing, and/or circumocular rash.

Photosensitivity has been reported in patients taking oral trimethoprim.

DOSAGE AND ADMINISTRATION:
Adults: In mild to moderate infections, instill one drop in the affected eye(s) every three hours (maximum of 6 doses per day) for a period of 7 to 10 days.

Pediatric Use: Clinical studies have shown trimethoprim sulfate and polymyxin B sulfate ophthalmic solution to be safe and effective for use in children over two months of age. The dosage regimen is the same as for adults.

HOW SUPPLIED:
Trimethoprim Sulfate and Polymyxin B Sulfate Ophthalmic Solution, containing 1mg trimethoprim and 10,000 polymyxin B units per mL, is supplied in a plastic bottle with a controlled drop tip in the following size:
10 mL (NDC 24208-315-10) - AB31509

DO NOT USE IF IMPRINTED NECKBAND IS NOT INTACT.

Storage: Store at 15°-30°C (59°-86°F). PROTECT FROM LIGHT.

Caution: Federal law prohibits dispensing without prescription.

Bausch & Lomb
Pharmaceutical Division
Tampa, Florida 33637

X050209 Rev. 5/96-6E

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064120

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 5

2. AADA # 64-120

3. NAME AND ADDRESS OF APPLICANT

Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa, FL 33637

4. BASIS OF SUBMISSION

The reference drug product is Polytrim Ophthalmic Solution Sterile, manufactured by Burroughs Wellcome Company (NDA #50567, Oct. 20, 1988).

21 CFR 448.330 provides for Polymyxin B sulfate-trimethoprim hemisulfate ophthalmic solution.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Trimethoprim Sulfate and Polymyxin B Sulfate Ophthalmic Solution, 1 mg (base)/10,000 units per mL.

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Date of Application: December 31, 1993
Date of Receipt: January 14, 1994
Date Acceptable for Filing: March 3, 1994
Amendment dated March 1, 1994
New Correspondence dated February 4, 1994
New Correspondence dated January 12, 1994
Refusal to file letter dated February 9, 1994.
Amendment dated October 24, 1994
Amendment dated September 16, 1994
Amendment dated April 4, 1995
Amendment dated March 20, 1995
Amendment dated May 28, 1996

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Ophthalmic Solution

14. POTENCY
Trimethoprim 1.0 mg (base)/mL
Polymyxin B Sulfate 10,000 Units/mL

15. CHEMICAL NAME AND STRUCTURE
Trimethoprim. 5-[3,4,5-Trimethoxyphenyl)methyl]-2,4-pyrimidinediamine; 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine. $C_{14}H_{18}N_4O_3$; mol wt 290.32

Polymyxin B Sulfate. a sulfate salt of a kind of polymyxin, a substance produced by the growth of Bacillus polymyxa (Prazmowski) Migula (Fam. Bacillaceae), or a mixture of two or more such salts.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
N/A

18. CONCLUSIONS AND RECOMMENDATIONS
The application may be approved.

19. REVIEWER:
V.Walton

DATE COMPLETED:
12/27/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064120

BIOEQUIVALENCE REVIEW(S)

FILE

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #64-120
SPONSOR: Bausch & Lomb Pharmaceuticals
DRUG: Trimethoprim, Polymyxin B Sulfates
DOSAGE FORM: Ophthalmic Solution (Sterile)
STRENGTH: EQ 1.0 mg base/mL; 10,000 Units/mL
REFERENCE PRODUCT: Polytrim® Ophthalmic Solution Sterile, manufactured by Burroughs Wellcome Company.
SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Trimethoprim, Polymyxin B Sulfates, Ophthalmic Solution Sterile; EQ 1.0 mg base/mL; 10,000 Units/mL is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug Polytrim® Ophthalmic Solution Sterile, manufactured by Burroughs Wellcome Company.

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III

INITIAL:_____ DATE: 10/23/1996

GROUP LEADER: Ramakant Mhatre, Ph.D. BRANCH: III

INITIAL:_____ DATE: 10/23/96

ACTING DIRECTOR: Rabindra Patnaik, Ph.D.
DIVISION OF BIOEQUIVALENCE

INITIAL:_____ DATE: 10/25/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL:_____ DATE:_____

APR 22 1994

Trimethoprim, Polymyxin B Sulfates,
Ophthalmic Solution (Sterile)
AADA #64120
Reviewer: Z.Z. Wahba
wp #64120w.D93

Bausch & Lomb Pharmaceuticals
Tampa, FL
Submission Date:
Dec. 31, 1993

REVIEW OF A WAIVER REQUEST

OBJECTIVE

The firm has requested a waiver of in vivo bioavailability study requirements for its drug product, Trimethoprim, Polymyxin B Sulfates, Ophthalmic Solution (Sterile), EQ 1.0 mg base/mL; 10,000 Units/mL. The reference drug product is Polytrim® Ophthalmic Solution Sterile, manufactured by Burroughs Wellcome Company (NDA #50567, Oct. 20, 1988).

INTRODUCTION

Trimethoprim is a synthetic antibacterial drug, active against a wide variety of aerobic gram-positive and gram-negative ophthalmic pathogens. Trimethoprim blocks the production of tetrahydrofolic acids by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. Polymyxin B, a cyclic lipopeptide antibiotic, is rapidly bactericidal for a variety of gram-negative organisms, specially Pseudomonas aeruginosa. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.

FORMULATION COMPARISON

Ingredients	TEST mg/mL	[a]REFERENCE mg/mL
Trimethoprim	1.00	1.00
Polymyxin B Sulfate, USP	10,000 U/gm	10,000 U/gm
Sodium Chloride, USP		
Benzalkonium Chloride, NF		
Sodium Hydroxide, NF	pH adjust	pH adjust
Sulfuric Acid, NF	pH adjust	pH adjust
Purified Water, USP	qs	qs

[a]The reference drug product formula should not be released through freedom of information.

COMMENTS

1. Both the test (Trimethoprim, Polymyxin B Sulfates, Ophthalmic Solution Sterile, EQ 1.0 mg base/mL; 10,000 Units/mL, manufactured by Bausch & Lomb Pharmaceuticals) and reference (Polytrim® Ophthalmic Solution Sterile, manufactured by Burroughs Wellcome Company) products are identical in formulation.

2. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(2). The test drug product is a topically applied preparation intended for local

therapeutic effect.

RECOMMENDATIONS

The Division of Bioequivalence agrees that the information submitted by Bausch & Lomb Pharmaceuticals on its drug product, Trimethoprim, Polymyxin B Sulfates, Ophthalmic Solution Sterile, EQ 1.0 mg base/mL; 10,000 Units/mL falls under 21 CFR section 320.22(b)(2) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems Trimethoprim, Polymyxin B Sulfates, Ophthalmic Solution Sterile, EQ 1.0 mg base/mL; 10,000 Units/mL, manufactured by Bausch & Lomb Pharmaceuticals to be bioequivalent to the reference drug product, Polytrim® Ophthalmic Solution Sterile, manufactured by Burroughs Wellcome Company.

The firm should be informed of the recommendations.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED MPARK
FT INITIALLED MPARK 4/22/94

cc: AADA #64-120, (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-658 (Park, Wahba), Drug File, Division File.
ZZWahba/41994/wp #64120w.d93